

Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects

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ABSTRACT

BACKGROUND: After no research in humans for >40 years, there is renewed interest in using lysergic acid diethylamide (LSD) in clinical psychiatric research and practice. There are no modern studies on the subjective and autonomic effects of LSD, and its endocrine effects are unknown. In animals, LSD disrupts prepulse inhibition (PPI) of the acoustic startle response, and patients with schizophrenia exhibit similar impairments in PPI. However, no data are available on the effects of LSD on PPI in humans.

METHODS: In a double-blind, randomized, placebo-controlled, crossover study, LSD (200 µg) and placebo were administered to 16 healthy subjects (8 women, 8 men). Outcome measures included psychometric scales; investigator ratings; PPI of the acoustic startle response; and autonomic, endocrine, and adverse effects.

RESULTS: Administration of LSD to healthy subjects produced pronounced alterations in waking consciousness that lasted 12 hours. The predominant effects induced by LSD included visual hallucinations, audiovisual synesthesia, and positively experienced derealization and depersonalization phenomena. Subjective well-being, happiness, closeness to others, openness, and trust were increased by LSD. Compared with placebo, LSD decreased PPI. LSD significantly increased blood pressure, heart rate, body temperature, pupil size, plasma cortisol, prolactin, oxytocin, and epinephrine. Adverse effects produced by LSD completely subsided within 72 hours. No severe acute adverse effects were observed.

CONCLUSIONS: In addition to marked hallucinogenic effects, LSD exerts methylenedioxymethamphetamine-like empathogenic mood effects that may be useful in psychotherapy. LSD altered sensorimotor gating in a human model of psychosis, supporting the use of LSD in translational psychiatric research. In a controlled clinical setting, LSD can be used safely, but it produces significant sympathomimetic stimulation.

Keywords: Adverse effects, Hormones, LSD, Prepulse inhibition, Subjective effects, Sympathomimetic effects

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Lysergic acid diethylamide (LSD) is a prototypical classic hallucinogen (1,2). The psychotropic effects of LSD were discovered in 1943 by Hofmann in Basel (3). In the 1950s–1970s, LSD was initially used as an experimental tool (“psychotomimetic”) to study psychotic-like states and model psychosis (4,5) and as an adjunct in “psychoalytic psychotherapy.” It has also been investigated for the treatment of alcoholism (6), addiction (7), cluster headache (8), and anxiety associated with terminal illness (9–11). Today, LSD is used illicitly for recreational (personal or spiritual) purposes. The lifetime prevalence of LSD use among adults is 6%–8% (12,13). Despite the widespread recreational use, no experimental scientific pharmacologic studies have been conducted with LSD in the last 40 years, until recently (14). After the initial psychiatric investigation by Stoll (15), several case reports and studies in the 1950s and 1960s described aspects of the psychological effects of LSD (5,16–18). However, these studies were not performed according to current research standards and did not include control conditions or the systematic characterization of psychotropic effects. Many studies also

sought to describe the psychotomimetic effects of LSD but were not designed to measure any positive subjective effects. Modern experimental studies with hallucinogens in humans resumed in the 1990s with *N,N*-dimethyltryptamine (DMT; also known ayahuasca) (19–22), ketamine (22–24), and psilocybin (25,26), but not with LSD. More recently, LSD and psilocybin have been evaluated in pilot therapeutic studies as treatments for anxiety in patients with life-threatening diseases (11,27). Because of the continued popularity of LSD as a recreational drug and renewed interest in its therapeutic use (11,28), we re-examined the acute response to LSD in healthy subjects. To allow for a better characterization of the subjective effects of LSD, we used psychometric instruments that have been used with other psychotropic drugs, including hallucinogens, empathogens, and stimulants (21,22,29–32).

Serotonergic hallucinogens, including psilocybin, DMT, and LSD, elicit mostly visual perceptual disturbances that resemble perceptual disturbances observed in early schizophrenia (22,33–35). Hallucinogens also induce alterations in information processing that are similar to those observed in

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schizophrenia. Specifically, prepulse inhibition (PPI) of the acoustic startle response serves as an operational measure of sensorimotor gating that can be assessed in animals and humans (36). In schizophrenia, PPI is impaired in prodromal states and early phases (36–39), and hallucinogens such as LSD acutely disrupt PPI in animals (40–45). In animals, PPI serves as a preclinical model of schizophrenia (46). The effects of LSD on sensorimotor gating function have not yet been explored in humans and were tested in the present study. We hypothesized that LSD would produce alterations in waking consciousness and impair PPI. Additionally, no data are available on the acute autonomic and adverse effects of LSD, and the endocrine effects of LSD in humans are unknown. Up-to-date clinical safety data are mostly missing. Because of the continued popularity of LSD as a recreational drug and interest in its therapeutic use, we also examined the acute somatic and endocrine response to LSD.

METHODS AND MATERIALS

Participants

We recruited 16 healthy subjects (8 men, 8 women; mean age \pm SD, 28.6 \pm 6.2 years; range, 25–51 years) by word of mouth or an advertisement placed on the web market platform of the University of Basel. All subjects provided written informed consent and were paid for their participation. Additionally, we considered the safety recommendations for high-dose hallucinogen research (47,48). The participant characteristics are described in detail in [Supplement 1](#). Seven subjects had used a hallucinogen one to three times, and another four subjects had prior experience with methylenedioxymethamphetamine (MDMA) (two to four times).

Study Design

A double-blind, placebo-controlled, crossover design was used with two experimental test sessions in balanced order. The washout periods between sessions were at least 7 days. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the Ethics Committee of the Canton of Basel, Switzerland, and Swiss Agency for Therapeutic Products (Swissmedic). The administration of LSD to healthy subjects was authorized by the Swiss Federal Office for Public Health, Bern, Switzerland. The study was registered at [ClinicalTrials.gov](#) (NCT01878942).

Drugs

Administration of LSD was in a single absolute dose of 200 μ g, corresponding to a dose of 2.84 \pm .13 μ g/kg body weight (mean \pm SEM; range, 2.04–3.85 μ g). The same dose was used in LSD-assisted psychotherapy in a clinical study (11). The dose was within the range of doses taken for recreational purposes and expected to induce robust effects in humans (1). The drug preparation is described in [Supplement 1](#).

Study Procedures

The study included a screening visit with the study physician, a separate psychiatric interview, an additional visit with the

study physician for familiarization, two 25-hour test sessions, and an end-of-study visit. The sessions were conducted in a calm laboratory environment. Only one research subject and one or two investigators were present during the test sessions. The test sessions began at 8:15 AM. A urine sample was taken to verify abstinence from drugs of abuse, and a urine pregnancy test was performed in women, and all subjects underwent baseline measurements. LSD (200 μ g) or placebo was administered at 9:00 AM. The outcome measures were repeatedly assessed for 24 hours. A standardized lunch and dinner were served at 1:30 PM and 5:30 PM, respectively. The subjects were under constant supervision by the study physician until 1:00 AM. The subjects were never alone during the first 16 hours after drug administration, and the investigator was in a room next to the subject for up to 24 hours. The subjects were sent home the next day at 9:30 AM.

Subjective Drug Effects

Subjective measures included scores on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale (29,49), visual analog scales (VASs) (50), the Adjective Mood Rating Scale (AMRS) (51), and the Addiction Research Center Inventory (ARCI) (31). The 5D-ASC scale is designed to be used retrospectively and was administered 24 hours after drug administration to rate the peak drug effects. The VASs were administered repeatedly for up to 24 hours to assess drug effects over time. The AMRS and ARCI were administered before and 3, 10, and 24 hours after drug administration. The procedures are described in detail in [Supplement 1](#).

Acoustic Startle Response Measurement

The eye-blink component of the acoustic startle response was measured using an electromyographic startle system (EMG-SR-Lab; San Diego Instruments, San Diego, California) as described in detail elsewhere (36) and in [Supplement 1](#). Briefly, the session included 16 pulse-alone stimuli (115 dB) and 32 similar pulse trials that were preceded by a 20-msec prepulse (86 dB) and an interstimulus interval (ISI) of 30, 60, 120, or 2000 msec, resulting in four prepulse trial conditions.

Cardiovascular, Autonomic, Adverse, and Endocrine Effects

Cardiostimulant (blood pressure and heart rate), autonomic (body temperature and pupillary function), psychomotor performance, endocrine measures (plasma cortisol, prolactin, oxytocin, norepinephrine, and epinephrine), and adverse effects were measured as described in [Supplement 1](#).

Data Analysis

The data were analyzed using STATISTICA Version 12 software (StatSoft, Inc, Tulsa, Oklahoma). Peak or peak change from baseline values were determined for repeated measures. Data were analyzed using repeated-measures analysis of variance (ANOVA), with drug (LSD vs. placebo) as the within-subjects factor. The PPI data were analyzed using repeated-measures ANOVA, with drug and trial condition (30, 60, 120, and 2000 msec) as within-subjects factors, followed by direct

comparisons for each trial condition. Modulatory effects of sex and hallucinogen experience were evaluated by including the respective between-subjects factor into the ANOVA. Spearman's rank correlations were used to determine associations between measures. The criterion for statistical significance was $p < .05$.

RESULTS

Subjective Drug Effects

Altered States of Consciousness on the 5D-ASC. Pronounced alterations of waking consciousness were induced by LSD (Figure 1). Ratings of oceanic boundlessness [$F_{1,15} = 92.3, p < .001$] and visionary restructuralization [$F_{1,15} = 243.5, p < .001$] were most strongly increased by LSD. The elevated ratings for oceanic boundlessness indicated that LSD elicited a state of positively experienced derealization and depersonalization with predominantly increased ratings for "experience of unity" [$F_{1,15} = 60.2, p < .001$] and "blissful state" [$F_{1,15} = 68.1, p < .001$]. Additionally, LSD produced marked visionary restructuralization phenomena, including increased ratings for "elementary and complex imagery" [$F_{1,15} = 123.8, p < .001$, and $F_{1,15} = 55.9, p < .001$, respectively], "audiovisual synesthesia" [$F_{1,15} = 156.8, p < .001$], and "changed meaning of percepts" [$F_{1,15} = 93.3, p < .001$]. Only minimal "auditory alterations" [$F_{1,15} = 34.5, p < .001$] were induced by LSD. Also, LSD moderately increased ratings of anxious ego dissolution [$F_{1,15} = 16.1, p < .01$], mostly attributable to significantly increased ratings for "disembodiment" [$F_{1,15} = 34.4, p < .001$] and "impaired control and cognition" [$F_{1,15} = 25.3, p < .001$], but not "anxiety" [$F_{1,15} = 4.2, p = .06$]. Profound anxiety or panic

was not experienced by any subject. However, two subjects (one woman and one man) reacted with transient anxiety, including fear of losing control, which completely resolved without pharmacologic intervention within 2–3 hours. No sex differences were observed in the effects of LSD on the 5D-ASC scale.

Psychotropic Effects over Time on VASs. Subjective effects on the VASs are shown in Figure 2, and maximal effects are presented in Table S2 in Supplement 1. The subjective effects began 30–60 min after LSD administration. Peak effects (any drug effects) were reported after (mean \pm SD) $1.75 \pm .82$ hours. After 5 hours, the subjective effects of LSD gradually subsided, but effects lasted up to 12 hours after LSD administration. Three subjects rated the subjective effects >50% of maximal possible effects at 12 hours. Compared with placebo, LSD produced pronounced increases in all VAS ratings, including "any drug effects," "good drug effect," "drug high," "drug liking," and "stimulated" [all $F_{1,15} \geq 1931$, all $p < .001$]. Peak effects for "any drug effects," "good drug effect," and "drug liking" reached 90% of the maximal possible score. Additionally, LSD significantly increased ratings of "empathogenic" drug effects, including "happy," "closeness," "open," and "trust" [all $F_{1,15} \geq 34$, all $p < .001$]. LSD decreased subjective concentration [$F_{1,15} = 212.5, p < .001$]. Compared with placebo, LSD induced small but significant increases in "bad drug effect" and "fear" [$F_{1,15} = 23.9, p < .001$, and $F_{1,15} = 13.2, p = .003$, respectively]. The subjective effects of LSD did not differ between sexes.

AMRS. On the AMRS, LSD significantly increased ratings of "well-being" [$F_{1,15} = 8.2, p < .05$], "emotional excitation"

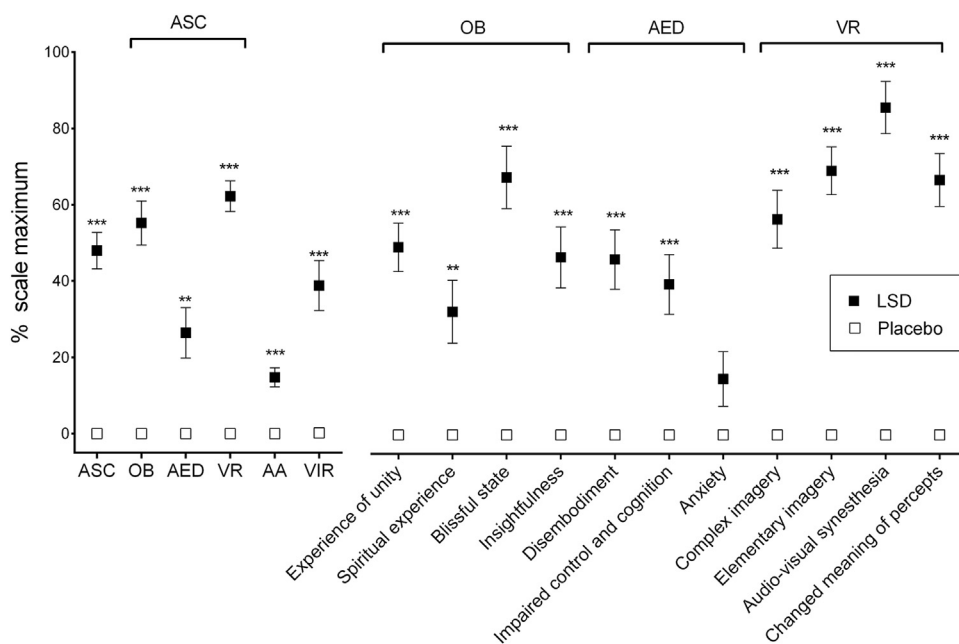


Figure 1. Effects of lysergic acid diethylamide (LSD) on the 5 Dimensions of Altered States of Consciousness scale. LSD predominantly increased ratings of oceanic boundlessness and visionary restructuralization. Increased oceanic boundlessness ratings mostly resulted from higher ratings for blissful state and experience of unity. Increases in visionary restructuralization ratings were attributable to high ratings for audiovisual synesthesia, elementary and complex imagery, and changed meaning of percepts. LSD produced only very little auditory alterations. LSD-induced increases in anxious ego dissolution were small because of elevated ratings for disembodiment, impaired control, and cognition but not anxiety. Vigilance was significantly reduced by LSD compared with placebo. The global Altered States of Consciousness score consists of the summation of the oceanic boundlessness, anxious ego dissolution, and visionary restructuralization scores. ** $p < .01$, *** $p < .001$ compared with placebo. Data are expressed as mean \pm SEM in 16 subjects. AA, auditory alterations; AED, anxious ego dissolution; ASC, Altered States of Consciousness; OB, oceanic boundlessness; VIR, vigilance; VR, visionary restructuralization.

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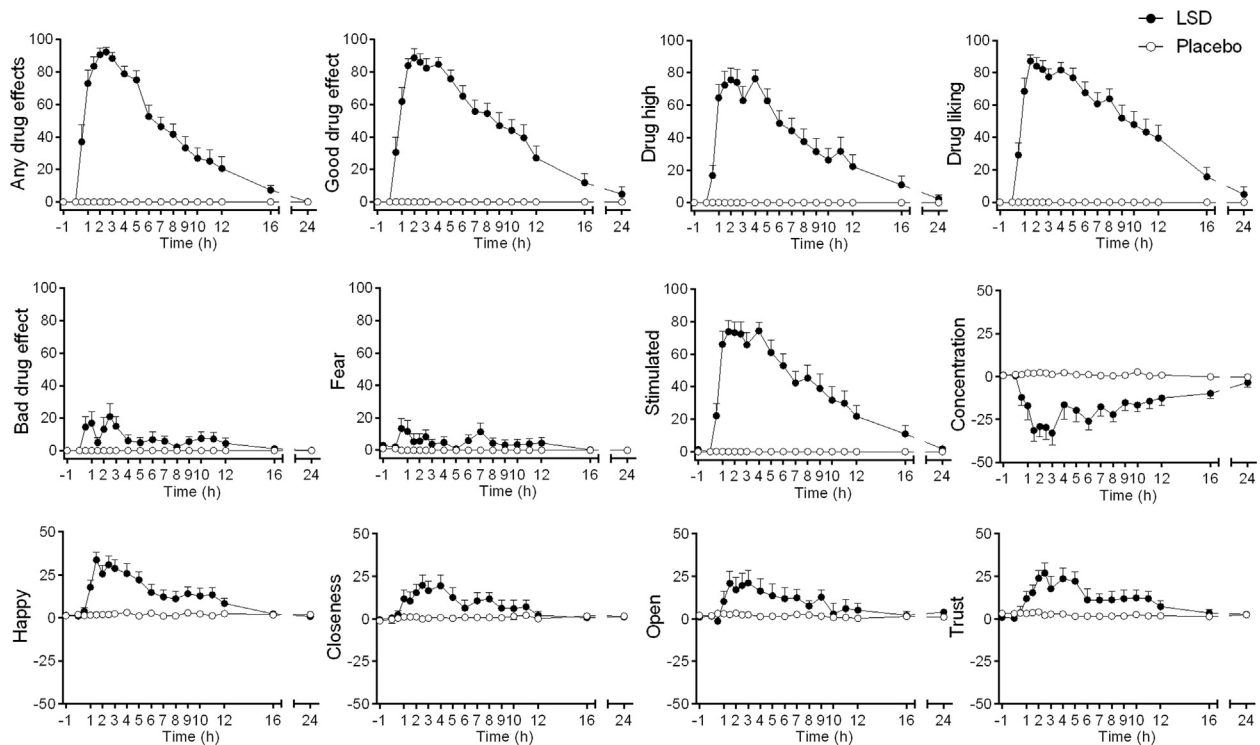


Figure 2. Subjective effects of lysergic acid diethylamide (LSD) over time on the visual analog scales. LSD or placebo was administered at $t = 0$ hours. The subjective effects began 30–60 min after LSD administration, peaked after 1–5 hours, gradually subsided after 5 hours, and were increased up to 12 hours. LSD produced significant changes in all visual analog scale ratings. However, “bad drug effects” and “fear” were only minimally elevated. LSD also increased ratings that are typically increased by empathogens, including ratings for “happy,” “closeness,” “open,” and “trust.” Data are expressed as mean \pm SEM % maximal values in 16 subjects.

$[F_{1,15} = 17.4, p < .001]$, “inactivity” $[F_{1,15} = 10.8, p < .01]$, “introversion” $[F_{1,15} = 16.9, p < .001]$, and “dreaminess” $[F_{1,15} = 57.9, p < .001]$ compared with placebo (Figure 3 and Table S2 in Supplement 1). Ratings of “extroversion” or “anxiety” were not altered by LSD. No sex differences were observed in the effects of LSD on the AMRS.

ARCI. Subjective effects on the ARCI are presented in Table S2 and Figure S1 in Supplement 1. LSD significantly increased ratings on the amphetamine group scale $[F_{1,15} = 15.8, p = .001]$, with a trend toward significantly reduced ratings on the benzedrine group scale $[F_{1,15} = 3.8, p = .07]$. Also, LSD significantly increased ratings of euphoria and drug liking on the morphine-benzedrine group scale $[F_{1,15} = 31.3, p < .001]$, sedation on the pentobarbital-alcohol group scale $[F_{1,15} = 52.6, p < .001]$, and ratings on the LSD group scale $[F_{1,15} = 24.4, p < .001]$, a measure of dysphoric and psychotomimetic changes. No sex differences were observed in the effects of LSD on the ARCI.

Investigator-Rated Drug Effects. The investigator-rated drug effects are shown in Table S2 and Figure S2 in Supplement 1. Investigator ratings of “any drug effect” $[F_{1,15} = 449.7, p < .001]$, “distance from reality” $[F_{1,15} = 21.7, p < .001]$, “happiness” $[F_{1,15} = 37.4, p < .001]$, and “non-speech vocalization” $[F_{1,15} = 6.9, p < .05]$ were increased by LSD. Ratings for “anxiety” or “paranoid thinking” were not

significantly increased. LSD did not alter the percentage of time “talking with the investigator” compared with placebo.

Acoustic Startle Response

The effects of LSD on PPI and startle response habituation are shown in Figure 4. The data from one participant were excluded because of technical reasons. The two-way ANOVA, with drug and prepulse trial condition as within-subject factors, revealed a significant drug \times prepulse trial interaction $[F_{3,42} = 3.0, p < .05]$. LSD significantly reduced PPI in the 30-msec and 60-msec trial conditions $[F_{1,14} = 5.5, p < .05, \text{ and } F_{1,14} = 5.1, p < .05, \text{ respectively}]$ and tended to reduce PPI in the 120-msec trial condition $[F_{1,14} = 3.4, p = .09]$ (Figure 3A). Compared with placebo, LSD nonsignificantly increased the startle response (mean reaction amplitude over all pulse-alone trials [mean \pm SD], 571 ± 321 units and 469 ± 190 units after administration of LSD and placebo, respectively). The two-way ANOVA for pulse-alone trials, with drug and block (time) as factors, showed a significant main effect of block, indicating habituation of the startle response over time $[F_{3,42} = 12.8, p < .001]$. No drug \times block interaction was observed, indicating similar habituation of the response over time in the LSD and placebo conditions (Figure 4B). Similarly, LSD did not affect percentage of habituation compared with placebo. No associations were found between percentage of PPI disruption and any subjective effect ratings assessed shortly before or after the startle measurement.

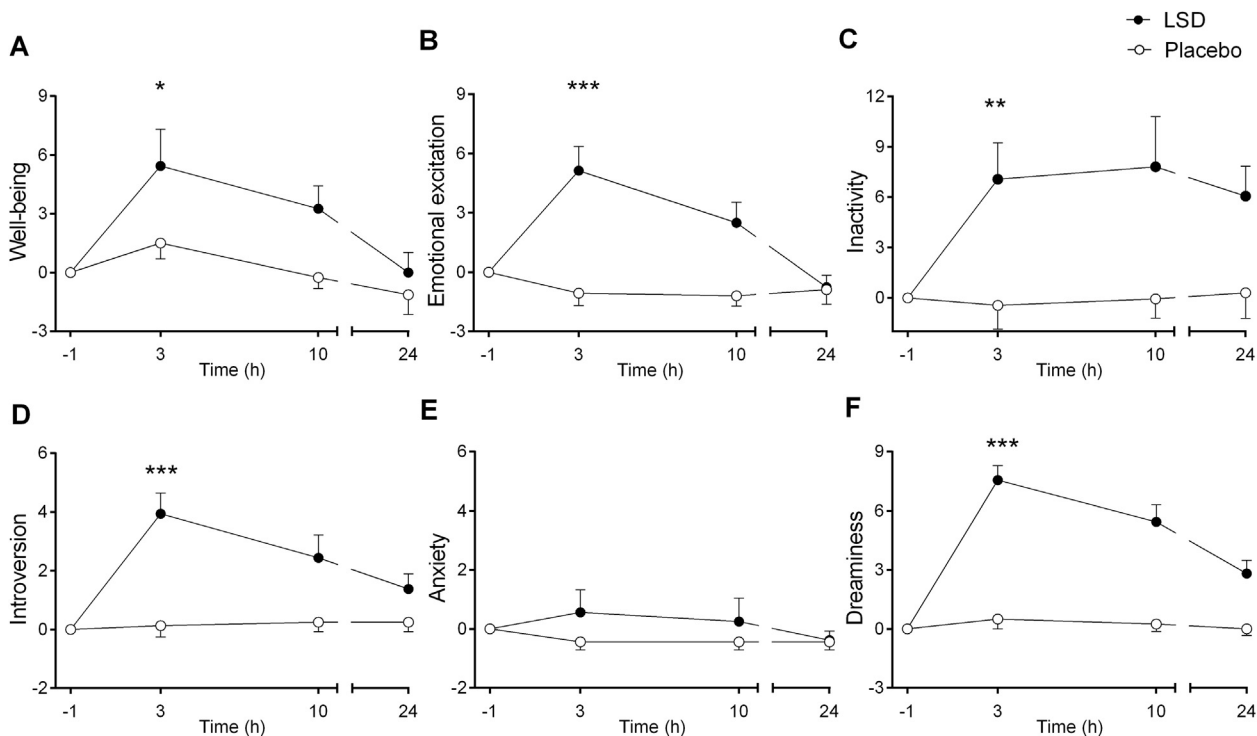


Figure 3. Subjective effects on the Adjective Mood Rating Scale. Lysergic acid diethylamide (LSD) or placebo was administered at t = 0 hours. LSD induced increases in general well-being (A), emotional excitation (B), inactivity (C), introversion (D), and dreaminess (F). LSD did not induce significant anxiety (E). Data are expressed as mean ± SEM change from baseline in 16 subjects. **p* < .05, ***p* < .01, ****p* < .001 compared with placebo.

Cardiovascular, Autonomic, Adverse, and Endocrine Effects

Peak values and statistics are shown in Table S2 in Supplement 1. Compared with placebo, LSD significantly increased systolic [$F_{1,15} = 23.77, p < .001$] and diastolic [$F_{1,15} = 25.19, p < .001$] blood pressure, heart rate [$F_{1,15} = 15.27, p = .001$], and body temperature [$F_{1,15} = 11.61, p = .004$] (Figure 5). LSD significantly increased the pupil size in the dark and after a light stimulus [$F_{1,15} = 22.71$ and $F_{1,15} = 36.33$, respectively, both $p < .001$] (Figure S3 in Supplement 1). Participants' ability to balance on one foot was significantly impaired by LSD [$F_{1,15} = 26.1, p = .001$] (Figure S4 in

Supplement 1). The plasma concentrations of cortisol [$F_{1,15} = 198.03, p < .001$], prolactin [$F_{1,15} = 10.13, p < .01$], oxytocin [$F_{1,15} = 9.40, p < .01$], and epinephrine [$F_{1,15} = 8.95, p < .01$] were significantly increased by LSD (Figure 6). Compared with placebo, LSD significantly increased the total acute (0–10 hours) [$F_{1,15} = 13.67, p < .01$] and subacute (10–24 hours) [$F_{1,15} = 7.19, p < .05$] adverse effects but not adverse effects at 24–72 hours. Adverse effects at 24–72 hours did not differ between LSD and placebo. The frequently reported acute adverse effects of LSD are presented in Table S3 in Supplement 1. There were no severe acute effects. The somatic and endocrine effects of LSD did not differ between sexes.

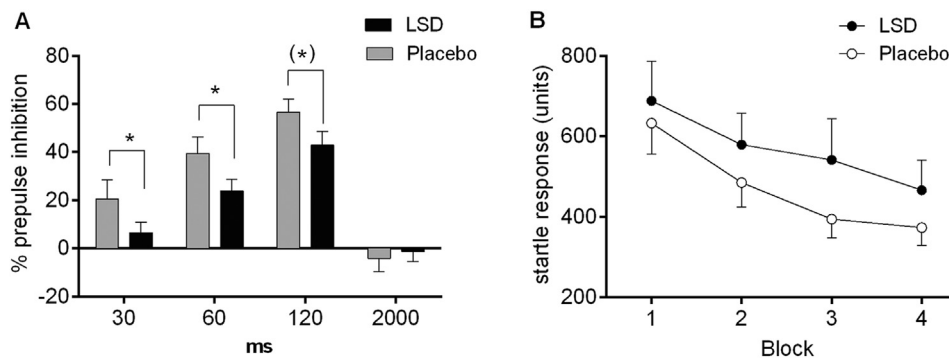


Figure 4. Effects of lysergic acid diethylamide (LSD) on the percentage of prepulse inhibition of the acoustic startle response (A) and startle response habituation over time (B). LSD significantly reduced percentage of prepulse inhibition in trials with prepulses that were presented 30 msec or 60 msec before the startle pulse compared with placebo (A). A trend toward a significant reduction of percentage of prepulse inhibition was observed for the 120-msec prepulse trial condition. LSD did not significantly alter the startle response or startle response habituation compared with placebo (B). Data are

expressed as mean ± SEM in 15 subjects. **p* < .05, ([†])*p* = .09 compared with placebo.

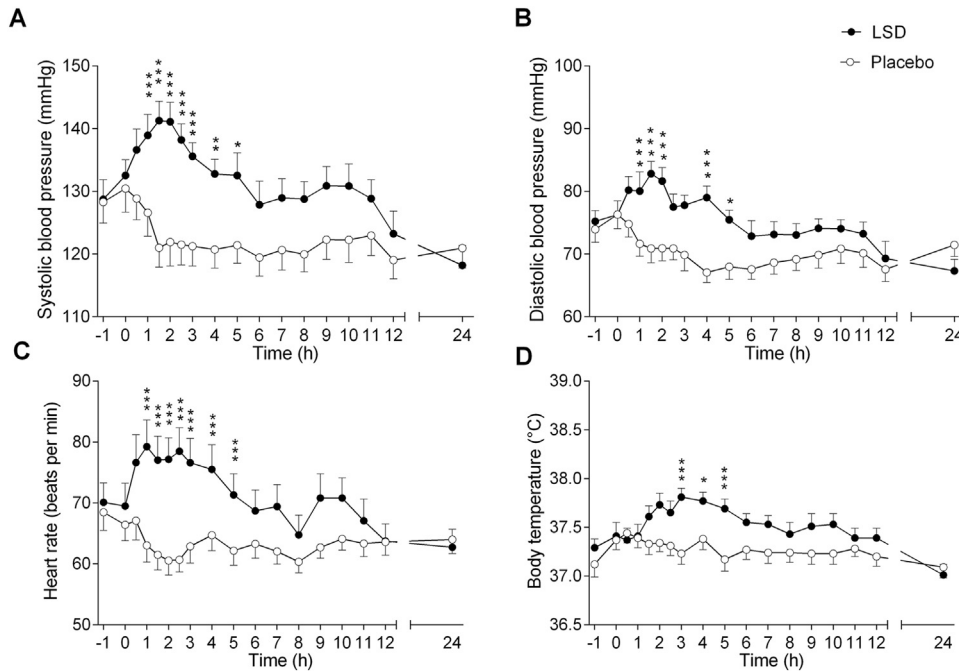


Figure 5. Effect of lysergic acid diethylamide (LSD) on vital signs. LSD or placebo was administered at $t = 0$ hours. LSD significantly increased systolic (A) and diastolic (B) blood pressure, heart rate (C), and body temperature (D) compared with placebo. Comparisons for each time point revealed that the cardiostimulant (A, B) and thermogenic (D) changes induced by LSD were significant up to 5 hours after drug administration compared with placebo, but moderate trend changes remained up to 11 hours before the levels returned to baseline. Data are expressed as mean \pm SEM in 16 subjects. * $p < .05$, ** $p < .01$, *** $p < .001$ compared with placebo.

DISCUSSION

The subjective effects of LSD began 30–60 min after administration and peaked at 1.75 hours but remained high for 3–5 hours before gradually declining. LSD induced a pronounced alteration in waking consciousness, including visual perceptual alterations, audiovisual synesthesia, and positively experienced derealization and depersonalization. LSD did not

induce pronounced anxiety and overall produced high ratings of good drug effects and low ratings of bad drug effects. Feelings of well-being, happiness, closeness to others, openness, and trust were also increased by LSD, effects typically associated with the empathogen MDMA (Ecstasy) (52).

The acute psychological effects of LSD lasted 12 hours in most subjects and up to 16 hours in some, which is longer

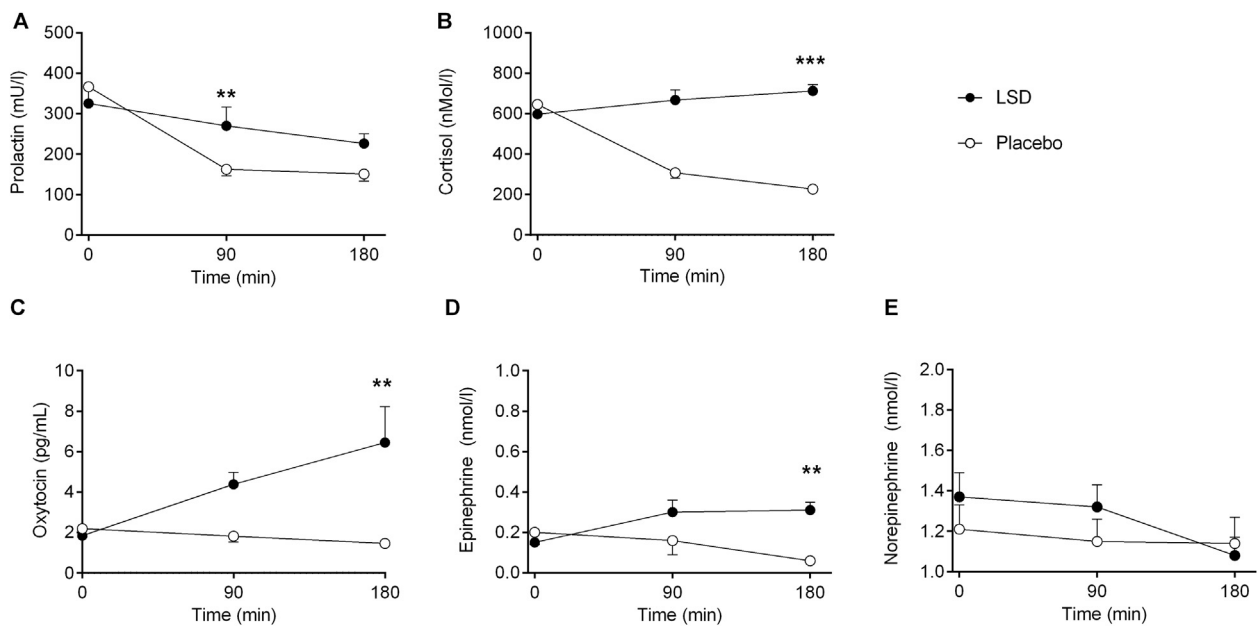


Figure 6. Endocrine effects of lysergic acid diethylamide (LSD). LSD significantly increased the plasma concentrations of prolactin (A), cortisol (B), oxytocin (C), and epinephrine (D). LSD did not significantly alter the plasma levels of norepinephrine (E). LSD or placebo was administered at $t = 0$ min. Data are expressed as mean \pm SEM in 16 subjects. ** $p < .01$, *** $p < .001$ compared with placebo.

than the 6–10 hours or 12 hours reported by other authors (1,17,53); this could be attributable to the relatively high dose of LSD or more sensitive psychometric measures used in the present study. The effects of LSD lasted twice as long as the effects of psilocybin (6 hours) (54,55), lasted longer than the effects of DMT (<1 hour) (19), and possibly lasted a similar duration as the effects of mescaline (18,56).

In the present study, LSD produced higher scores on the 5D-ASC scale compared with psilocybin in a similar population of healthy subjects (55). In particular, LSD produced 30% higher ratings for oceanic boundlessness (mostly blissful state), 30% higher ratings for anxious ego dissolution, and 63% higher ratings for visionary restructuralization (mostly greater audiovisual synesthesia) compared with a high dose of psilocybin (55,57). Compared with DMT and ketamine, LSD produced 50% higher ratings for oceanic boundlessness, 50% higher ratings for visionary restructuralization, and comparably high ratings for anxious ego dissolution (22,29). On the AMRS, LSD produced similar ratings for emotional excitation, inactivation, and dreaminess compared with high-dose psilocybin (55). Similar to LSD, mean group anxiety scores were not appreciably increased by psilocybin (55). On the ARCI, LSD increased ratings on the amphetamine group scale and morphine-benzedrine group scale, suggesting stimulant and euphoric subjective effects that were similar to MDMA (58). In contrast, LSD reduced ratings on the benzedrine group scale, suggesting reduced energy and focus (58). LSD had overall similar effects to psilocybin on the ARCI (59). Subjective VAS ratings for happy, open, closeness to others, and trust were increased by LSD. Similarly, the investigators rated subjects as being happier after administration of LSD compared with placebo. Similar subjective effects are typically produced by empathogens, such as MDMA, but not by stimulants (30,60).

Altogether, the psychometric findings indicate that LSD produced stronger perceptual alterations than the doses of other psychotropic drugs tested so far as well as MDMA-like empathogenic mood effects. Additionally, LSD increased plasma oxytocin levels. Oxytocin is thought to contribute to the empathogenic and prosocial effects of MDMA (61) and may have similar effects in the case of LSD. Although LSD and MDMA were not compared in the same subjects, the present findings indicate that LSD exerts partially MDMA-like empathogenic effects that may be associated with common serotonergic or oxytocinergic properties (52). MDMA produces weak LSD-like perceptual alterations, likely via similar 5-hydroxytryptamine 2A (5-HT_{2A}) receptor stimulation (62). Pharmacologically, LSD acts as a direct partial agonist at serotonergic receptors (2,63), whereas MDMA mostly acts as an indirect serotonergic agonist by releasing serotonin via the serotonin transporter (64).

The primary safety concerns with hallucinogen research are psychological rather than somatic adverse effects (1). In laboratory studies that use psilocybin, ketamine, or MDMA, moderate anticipatory anxiety is common at the beginning of the onset of the drug's effects (49,65,66). Acute anxiety was also infrequently reported when LSD was administered at the same dose as the one used in the present study for LSD-assisted psychotherapy in patients with anxiety associated with life-threatening diseases (11). In the present study, LSD

produced anxiety in two subjects, which resolved spontaneously with verbal support from the investigators. Anxiety was related to fear of loss of thought control, disembodiment, and loss of self as similarly described for psilocybin (55). Some subjects also had to be reminded of the transient state of the drug-induced experience. None of the subjects had a current or past history of major psychiatric disorders, and all were well informed about the setting and acquainted with and constantly supervised by the same investigator. Also, only half of the subjects in the present study were hallucinogen-naïve, and the other half had very limited prior experience with hallucinogenic drugs. We found no differences in the quality and extent of the response to LSD between the hallucinogen-naïve and moderately experienced subjects. Consistent with this finding, prior experience with hallucinogenic drugs affected the response to psilocybin only moderately in a similar research setting (66).

In line with our hypothesis, LSD disrupted PPI and produced sensorimotor deficits similar to deficits observed in schizophrenia (36–39). In animals, LSD (40–42) and other serotonergic hallucinogens (43–45) reduce PPI. Also, LSD potentiated the startle magnitude and impaired habituation of the startle response in rats (67). Similar deficits in habituation were reported in patients with schizophrenia (36,38). Consistent with the preclinical findings, LSD reduced PPI in the present study at the 30–120 msec ISI. The startle response amplitude or its habituation was not significantly altered by LSD. Psilocybin reduced PPI at a short ISI (30 msec), had no effect at a medium ISI (60 msec), and increased PPI at long ISIs (120–2000 msec), without changing startle reactivity or habituation (68,69). The effects of LSD and psilocybin on the acoustic startle response and its modulation were quite similar. Additionally, the disruption of PPI induced by psilocybin in humans at a short ISI (30 msec) was prevented by administration of a 5-HT_{2A} receptor antagonist (70), consistent with similar preclinical studies of LSD (42). In contrast to the findings with LSD and psilocybin, DMT or ayahuasca had no effects on PPI, startle reactivity, or habituation in humans (20,71). Altogether, the effects of LSD on PPI in normal humans were consistent with the PPI deficits after LSD administration in animals and sensorimotor gating deficits in patients with schizophrenia.

Serotonergic hallucinogens, including LSD, are hypothesized to act at the 5-HT_{2A} receptor (2,54), which is upregulated in patients with schizophrenia (72). Genetic variations in the 5-HT_{2A} receptor gene influence PPI (73), and PPI deficits induced by psilocybin in humans depend on 5-HT_{2A} receptor stimulation (70). In animals, LSD disrupts PPI (40–42) also via 5-HT_{2A} receptor stimulation (42). To characterize further the role of 5-HT₂ receptors and other receptors in the subjective and sensorimotor psychotomimetic effects of LSD in humans, future studies should investigate the effects of receptor antagonists on the response to LSD using a similar experimental setting. The present findings lend support to the use of LSD to study the neurobiological basis of psychotic states in humans. To date, brain activation patterns have not been studied using LSD in neuroimaging studies, in contrast to several modern investigations that used psilocybin to model psychotic states (25,26).

Significant sympathomimetic effects, including increases in blood pressure, heart rate, and pupil size, were produced by

LSD. Similar findings were reported in early studies in the 1950s (74–78). In contrast, LSD (200 µg administered orally) did not alter diastolic or systolic blood pressure or heart rate in a recent study in eight patients with different chronic life-threatening illnesses (11). Overall, the cardiostimulant effects of LSD were moderate and smaller than the effects seen with empathogens and stimulants (30). The LSD-induced increase in epinephrine levels in the present study was similar to the effect produced by MDMA (79).

Body temperature was increased by LSD in the present study. In animals, LSD is thermogenic (80), and hyperthermia has been reported to be a consequence of massive LSD overdose in humans (81). Other serotonergic hallucinogens, including psilocybin and DMT, produce similar cardiostimulant and autonomic responses to LSD (18,55,59,82–84).

In the present study, LSD increased circulating levels of cortisol and prolactin. LSD binds to dopaminergic D₂ receptors (85). Studies in rats showed that LSD inhibited prolactin secretion by rat pituitary cells (86) and decreased plasma levels of prolactin in rats (87). These findings led to the suggestion that LSD acts as a dopamine D₂ receptor agonist in the pituitary. However, the present study in humans found that LSD increased the plasma levels of prolactin and cortisol, which are markers of serotonergic activity (88,89). Our findings suggest that the serotonergic stimulant effects of LSD on prolactin regulation usurp any dopamine D₂ receptor-mediated inhibition in humans at the dose used in the present study. Other serotonergic drugs, including psilocybin (55), DMT (84), ayahuasca (90), and MDMA (30,91), increased the plasma levels of prolactin and cortisol in humans.

The present study has several limitations. First, we used only a single dose of LSD, and we cannot provide dose-response data. We used a relatively high dose of LSD (200 µg), which produced a full and representative LSD response (1). The same dose of LSD was also used recently in patients with anxiety associated with terminal illness (11). Second, although we used formal blinding, the overt subjective effects of LSD unblinded the treatment assignment. Additionally, expectations may have influenced the psychological effects of LSD because all of the subjects knew that they would receive LSD or placebo and not another active drug. The psychological effects and risks of LSD are likely to be different from effects described herein if LSD is used recreationally in unsupervised settings or in subjects with psychiatric disorders. Third, endocrine measures were performed only at two time points during the expected peak drug effect, not allowing for a full characterization of the endocrine effects of LSD over a longer time interval.

In conclusion, LSD produced marked effects on perception and subjective effects on mood that were similar to effects reported for MDMA and increased plasma oxytocin, suggesting empathogenic properties that may be useful in psychotherapy (11). Consistent with preclinical data and the sensorimotor deficits seen in schizophrenia, LSD acutely decreased PPI of the acoustic startle response. The present experimental human study may serve as an interface for the translation of preclinical research with hallucinogens to clinical research findings in patients with schizophrenia and vice versa. Also, LSD may be useful for further study of alterations in consciousness and information processing in humans.

The present study showed that LSD can be safely administered in an experimental research setting in humans, forming a basis for further psychopharmacologic studies. However, the sympathomimetic stimulant effects need to be considered when LSD is to be used in patients with hypertension or heart disease.

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ClinicalTrials.gov: Psychological, Physiological, Endocrine, and Pharmacokinetic Effects of LSD in a Controlled Study; <http://clinicaltrials.gov/ct2/show/NCT01878942>.

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